W53

A Novel Disease-Modifying Strategy for Narcolepsy Type 1
Preclinical Rationale and Development Roadmap for the DOXA Platform:
Integrated Orexin Restoration and Translational Neuroprotective Development

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REFERENCES SCAN ME

Introduction

Narcolepsy type 1 (NT1), charaxcterized by an **excessive daytime sleepiness, cataplexy, REM dysregulation, sleep-wake instability**, is a chronic orphan neurological disorder caused by immune-mediated destruction of orexin/hypocretin-producing neurons within the lateral hypothalamus, resulting in profound orexin deficiency (CSF orexin-A ≤110 pg/mL).
NT1 is increasingly recognized as **a T-cell-mediated neuroinflammatory disease** occurring in genetically susceptible individuals, particularly carriers of the **HLA-DQB1*06:02 haplotype**, with additional involvement of **TCRα polymorphisms** and **cathepsin H-related pathways**.

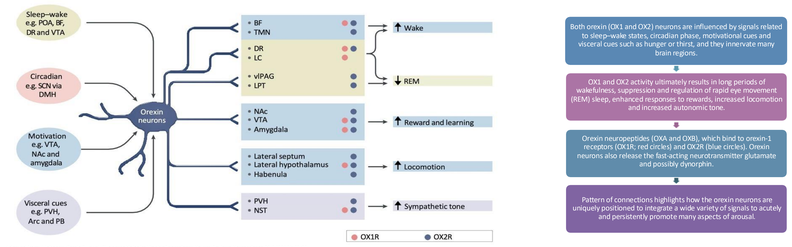
Current therapeutic development has largely focused on **selective OX2R agonists**, including TAK-861, ALKS-2680, ORX750, and E2086. Although these agents provide clinically meaningful wake-promoting effects, they may remain limited by incomplete REM regulation, insomnia liability, potential receptor desensitization associated with chronic high-affinity OX2R stimulation, and **absence of impact on the underlying orexin-neuron degeneration or neuroinflammatory process**.

Rational

Physiologically, endogenous **orexin signaling is mediated through both OX1R and OX2R receptors. OX2R is strongly involved in wake maintenance**, whereas **OX1R contributes to emotional arousal, REM boundary control, reward-circuit modulation, and cataplexy suppression** has historically been avoided because of theoretical concerns regarding reward-circuit activation and abuse liability, despite limited direct evidence demonstrating that balanced physiological OX1R/OX2R agonism induces clinically meaningful addictive behavior in humans.
This supports the hypothesis that **selective OX2R activation may only incompletely recapitulate the pathophysiological complexity** of endogenous orexin signaling, whereas **balanced dual OX1R/OX2R agonists** may more faithfully restore the broader biological functions of the orexin network, **including sustained wakefulness, REM regulation, emotional arousal processing, appetite and energy homeostasis, reward-related behaviors, autonomic balance, and overall sleep–wake organization.**

The **DOXA (Dual Orexin Receptor Agonist) platform** further extends beyond symptomatic wake promotion by **integrating additional neuroprotective and potentially disease-modifying mechanisms, including Cathepsin H (CTSH) modulation, neuroinflammatory regulation and potential metabolic reprogramming effects.** This multimodal pharmacological framework is supported by growing evidence that orexin dysfunction, chronic neuroinflammation, hypothalamic dysregulation, and impaired protein homeostasis represent interconnected pathological processes **not only in NT1**, but also across broader neurodegenerative and neuro-metabolic disorders.

Orexin Network and Neuroimmune Pathophysiology in NT1



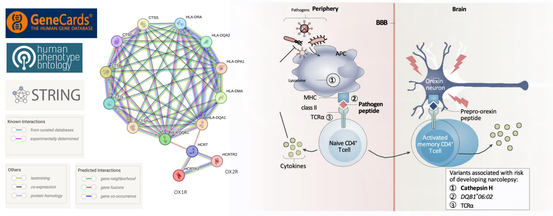
Adapted from: Mahoney, Carrie E., et al. The neurobiological basis of narcolepsy. Nature Reviews Neuroscience 20.2 (2019): 83-93.
Arc, arcuate nucleus; BF, basal forebrain; DMH, dorsomedial nucleus of the hypothalamus; DR, dorsal raphe; LC, locus coeruleus; LPT, lateral pontine tegmentum; NAc, nucleus accumbens; NST, nucleus of the solitary tract; PB, parabrachial nucleus; POA, preoptic area; PVH, paraventricular nucleus of the hypothalamus; SCN, suprachiasmatic nucleus; TMN, tuberomammillary nucleus; vlPAG, ventrolateral periaqueductal grey; VTA, ventral tegmental area.

Both orexin (OX1 and OX2) neurons are influenced by signals related to sleep-wake states, circadian phase, motivational cues and visceral cues such as hunger or thirst, and they innervate many brain regions.

OX1 and OX2 activity ultimately results in long periods of wakefulness, suppression and regulation of rapid eye movement (REM) sleep, enhanced responses to rewards, increased locomotion and increased autonomic tone.

Orexin neuropeptides (OXA and OXB), which bind to orexin-1 receptors (OX1R; red circles) and OX2R (blue circles). Orexin neurons also release the fast-acting neurotransmitter glutamate and possibly dynorphin.

Pattern of connections highlights how the orexin neurons are uniquely positioned to integrate a wide variety of signals to acutely and persistently promote many aspects of arousal.



In a possible model of T cell-mediated killing of orexin neurons, an antigen-presenting cell (APC) first takes up a pathogen and presents fragments of pathogen proteins (Cathepsin-H) to a naive CD4+ T cell using a major histocompatibility complex (MHC) class II molecule, perhaps DQB1*06:02.

The naive CD4+ T cell may secrete cytokines (circles) to help clear the infection. Memory CD4+ T cells are formed from the initial infection. Fever may promote the migration of pathogen-specific CD4+ T cells across the blood–brain barrier (BBB).

The activated memory CD4+ T cell cross-recognizes fragments of prepro-orexin with a similar epitope as the pathogen peptide and secretes cytokines that promote destruction of the orexin neurons.

Genes for which certain alleles are known to increase the risk of developing narcolepsy related to this model of T cell-mediated killing of orexin neurons are illustrated at their respective sites of action. TCR, T cell receptor.

Adapted from: Muñoz-Arteag, et al. The HLA-DQB1 gene and its relationship with narcolepsy NHUS (2018)
https://hla.arc/2018/the-hla-dqb1-gene-and-its-relationship-with-narcolepsy/

In the proposed **model of T-cell-mediated degeneration of orexin neurons**, antigen-presenting cells (APCs) first internalize pathogen-derived antigens through the endocytic pathway. Proteolytic processing within lysosomes—potentially involving **Cathepsin H (CTSH)—generates peptide fragments subsequently presented by MHC class II molecules such as HLA-DQ molecules to naïve CD4+ T cells**.
STRING network analyses further support functional interactions between HLA-associated immune pathways, cathepsin-related proteolytic systems, and orexin receptor signaling (HCRTR1/OX1R and HCRTR2/OX2R), reinforcing the concept that NT1 involves integrated neuroimmune dysregulation rather than isolated wakefulness circuitry dysfunction alone.
This evolving model provides the rationale for multimodal therapeutic strategies such as the DOXA platform, combining physiological orexin restoration with CTSH-related neuroinflammatory modulation.

Comparative Preclinical Effects of Dual OX1R/OX2R Agonists and Selective OX2R Agonists on NT1 Narcolepsy Models

Compound	Receptor Profile	Dose & Route	Animal Model (N)	Cataplexy Endpoint & Observation	Cataplexy Suppression	Wakefulness Increase	Wake Consolidation	REM / PS Effects	NREM / SWS Effects	Limitation
TAK-925 (danavorexton)	Selective OX2R agonist	3–10 mg/kg IV	Orexin/ataxin-3 mice (typically N=6–10/group in published studies)	Acute EEG/EMG recordings; ~2–3 h post-dose	~80–100% suppression during infusion window	Strong acute wake promotion; wake time approaching normal WT levels	Moderate wake consolidation; limited published fragmentation analyses	Partial REM suppression and reduction of REM intrusions	Limited quantitative SWS transition analyses publicly available	IV administration only; short PK exposure; translational dosing constraints
TAK-994	Selective OX2R agonist	3 mg/kg PO	Orexin-tTA; TetO-DTA mice (reported preclinical cohorts N=8–12/group)	Cataplexy episode frequency over ~6 h recording	~66.7% reduction (=9 to 3 episodes)	~71% wake increase vs vehicle	Moderate consolidation; partial reduction in vigilance fragmentation	Reduced REM intrusions; limited REM-transition kinetic analyses	Mild reduction in NREM fragmentation; detailed SWS architecture not fully disclosed	Hepatotoxicity / DILI signal terminated development
TAK-861 (oveporexton)	Selective OX2R agonist	1 mg/kg PO	OX/Ataxin-3 mice (typically N=7–10/group in preclinical reports)	Acute nocturnal assessment; ~2–4 h	~80% reduction in cataplexy-like events	~58% wake increase	Moderate-to-strong wake maintenance	Partial REM stabilization; REM fragmentation metrics incompletely reported	Limited published SWS consolidation analyses	Potential receptor desensitization with chronic selective OX2R activation
AEX-2	Dual OX1R/OX2R agonist	20 mg/kg IP +1% DMSO)	ORX-KO mice (N=4)	Continuous EEG/EMG/video; repeated 20-min bins over 4 h	~51–52% reduction in cataplexy episodes over 4 h; suppression maximal at ~60–120 min	25.0 ± 3.0 min wake/60 min (+34%)	Mild-to-moderate improvement in wake continuity; wake episodes: 25 ± 4.0 vs 28 ± 4.1 vehicle	Partial REM normalization; reduced REM duration and episodes in early post-dose phase	Partial SWS stabilization; limited reduction in transition instability	Solubility/formulation limitations; IP-only in current dataset
AEX-41	Dual OX1R/OX2R agonist	5 mg/kg IP	ORX-KO mice (N=4)	Continuous EEG/EMG/video over 4 h; temporal kinetic modeling	~76–88% reduction over 4 h; near-complete suppression at peak (~60 min)	31.3 ± 3.8 min wake/60 min (+68%)	Strong wake consolidation; wake episodes reduced to 22 ± 4.2; mean wake bout duration increased to 15.2 ± 3.3 min	Significant REM reduction and REM-state stabilization	SWS episode number reduced (80.5 ± 8.1 vs 100.7 ± 10.1 vehicle), suggesting reduced instability	None identified preclinically in acute studies
AEX-41	Dual OX1R/OX2R agonist	40 mg/kg PO	ORX-KO mice (N=4)	4 h EEG/EMG/video recordings with repeated 20-min interval analyses	Peak suppression ~88–100%; sustained suppression ~92% at 240 min	43.9 ± 4.7 min wake/60 min (+73%; p<0.005)	Very strong wake stabilization; wake episodes reduced to 15 ± 4.4; mean wake bout duration increased to 23.2 ± 4.9 min	REM duration reduced by ~10%; reduced REM fragmentation and REM intrusions	SWS duration reduced to 124 ± 12.4 min vs 143 ± 14.3 vehicle; ~15% reduction in SWS transition instability	Dose optimization ongoing; possible ceiling above 80 mg/kg
AEX-41	Dual OX1R/OX2R agonist	80 mg/kg PO	ORX-KO mice (N=4)	4 h EEG/EMG/video	Sustained suppression maintained but less optimal than 40 mg/kg	35.2 ± 3.4 min wake/60 min	Strong but less optimal consolidation than 40 mg/kg; possible saturation effect	REM modulation maintained but less selective	SWS episode profile approaches vehicle values, suggesting receptor saturation/ceiling effect	Potential supra-optimal exposure

Integrated Preclinical Development Program of the DOXA Platform

Study Plan Criteria	Food–Drug Interaction Fed vs Fasted Wistar Rat Wakefulness Model	Opioid Addiction Morphine Self-Administration in Sprague-Dawley Rats	Cocaine Reinforcement CPP in C57BL/6 Mice	ALS B6-hTDP43wt×A315T Mice	Neuronal death by up-regulated microglial CTSH in LPS-induced Neuroinflammation and Orexin-Neuron Vulnerability	α-Synuclein A53T Transgenic Mice Parkinson's Disease Model
Program	Food effect / oral translational robustness / NT1 clinical usability	Addiction / Abuse-liability / Reward-circuit modulation	Addiction / Reward conditioning / Abuse-liability differentiation	ALS / Neurodegeneration / Disease-modifying PoC	NT1/ Neuroinflammation / CTSH disease-modifying hypothesis	Parkinson's disease / α-synuclein neurodegeneration / disease-modifying PoC
Title	Investigation of food intake effects on AEX-41 and AEX-2 wake-promoting efficacy in a rat wakefulness model	Evaluation of AEX-41 and AEX-2 on opioid reinforcement in a rat morphine self-administration model	Assessment of AEX-41 and AEX-2 on cocaine-induced reinforcement in a mouse conditioned place preference model	Efficacy of AEX-635 and AEX-609 in the B6-hTDP43wt×A315T transgenic mouse model of ALS	Evaluation of AEX-41 and AEX-2 on narcoleptic symptoms and orexin-neuron vulnerability in an LPS-induced neuroinflammation model with CTSH activation	Evaluation of AEX compounds on α-synuclein-related neurodegeneration in A53T transgenic mice
Animal Model	Male Wistar rats tested under fasted versus high-fat-fed conditions	Male Sprague-Dawley rats, 250–300 g, trained for IV morphine self-administration	Male C57BL/6 mice, 8–10 weeks old	B6-hTDP43wt×A315T mice, Thy1-driven human TDP-43 WT + A315T mutation	C57BL/6J mice; optional WT or partial orexin-neuron injury model for orexin-neuron preservation readouts	α-synuclein A53T transgenic mice
Scientific Basis	Food intake may alter oral absorption, exposure, receptor competition, or wake-promoting efficacy of orexin agonists	OX1R is involved in reward salience, emotional arousal, and mesolimbic dopamine regulation; this study tests whether dual OX1R/OX2R agonist activity is non-reinforcing and may reduce opioid-seeking	Cocaine CPP evaluates contextual reward learning and mesolimbic dopamine-driven reinforcement; OX1R may regulate emotional reward salience	TDP-43 pathology, neuroinflammation, NfL elevation, motor decline, and motor neuron vulnerability are central ALS-relevant features	LPS-induced neuroinflammation can activate microglia and upregulate CTSH-related inflammatory pathways; NT1 is associated with immune-mediated orexin neuron loss	α-synuclein aggregation, neuroinflammation, mitochondrial dysfunction, proteostasis impairment, and dopaminergic network degeneration are central PD-relevant mechanisms
Key Model Advantages	Direct comparison of pharmacodynamic efficacy under fed and fasted states; supports clinical dosing flexibility; allows PK/PD integration	Gold-standard addiction model; quantifies active drug-seeking; allows progressive-ratio motivation and relapse-like reinstatement testing	Standard reward-conditioning paradigm; sensitive to cocaine reinforcement; allows extinction and reinstatement testing	Progressive motor decline from 8–10 weeks; plasma NfL elevation; TDP-43 cytoplasmic inclusions; no intestinal obstruction; lifespan >11–14 months	Links sleep-wake symptoms with inflammatory stress; allows EEG/EMG assessment plus CTSH, microglial and cytokine biomarkers	Progressive α-synuclein pathology; motor and non-motor phenotype; suitable for testing neuroinflammation, proteostasis, and neuroprotective mechanisms
Test Compounds	AEX-41 PO; AEX-2 IP initially, with oral AEX-2 formulation added once available	AEX-41 and AEX-2	AEX-41 and AEX-2	AEX-635 and AEX-609	AEX-41 and AEX-2	Next-generation DOXA candidates selected for CTSH, Sigma-1, mitochondrial and proteostasis profiles
Groups	6 groups (N=8-10) 1. Fasted + vehicle; 2. Fed + vehicle; 3. Fasted + AEX-41; 4. Fed + AEX-41; 5. Fasted + AEX-2; 6. Fed + AEX-2	5 groups (10–12) 1. Vehicle; 2. AEX-41 5 mg/kg PO; 3. AEX-41 40 mg/kg PO; 4. AEX-2 20 mg/kg IP; 5. Naltrexone 1 mg/kg SC	5 groups (10–12) 1. Vehicle + cocaine; 2. AEX-41 5 mg/kg PO + cocaine; 3. AEX-41 40 mg/kg PO + cocaine; 4. AEX-2 20 mg/kg IP + cocaine; 5. Comparator control, e.g. naloxone/naloxone-like control depending CRO protocol	6 groups (N=16) 1. Vehicle; 2–3. AEX-635 3 and 10 mg/kg BID; 4–5. AEX-609 3 and 10 mg/kg BID; 6. Riluzole 30 mg/kg QD	6 groups (N=10) 1. Saline + vehicle; 2. LPS + vehicle; 3. LPS + AEX-41 low dose; 4. LPS + AEX-41 high dose; 5. LPS + AEX-2; 6. LPS + anti-inflammatory comparator	5 groups (N=12–15) 1. Vehicle; 2. Low-dose AEX; 3. High-dose AEX; 4. Reference comparator; 5. WT control, if included
Inflammatory Induction	Not applicable	Not applicable	Not applicable	Not applicable; intrinsic ALS-related neuroinflammatory pathology	C57BL/6J mice were intraperitoneally injected with either 0.9% saline or lipopolysaccharide (LPS, 5 mg/kg). Immunohistochemistry (IHC) and in situ hybridization (ISH) were used to analyze expression and localization of CTSH in the brain.	Not required; intrinsic α-synuclein-driven neurodegenerative pathology
Treatment Start	1 h after high-fat meal in fed groups; matched timing in fasted groups	After stable morphine self-administration, defined as >20 infusions/session	30 min before cocaine conditioning sessions	8 weeks of age, pre-symptomatic / very early symptomatic	Preventive arm: before LPS; therapeutic arm: after LPS inflammatory activation	Pre-symptomatic or early symptomatic phase
Treatment Duration	Acute 4 h pharmacodynamic recording; optional repeated dosing arm	7 consecutive treatment days	8 conditioning days, followed by test day and optional reinstatement phase	Until humane endpoint, full survival study	Acute 4 h EEG/EMG phase plus 24–72 h biomarker phase; optional 7–28 day subchronic follow-up	8–16 weeks depending on phenotype onset and CRO protocol
Primary Endpoints	Wake latency, total wake duration, wake episode duration	Morphine infusions/session; active lever presses	Time spent in cocaine-paired chamber; CPP preference score	Grip strength; rotarod latency; gait; body weight; plasma NfL	Wake duration; cataplexy burden; REM/PS instability; SWS fragmentation; CTSH expression/activity	Motor function, rotarod, pole test, grip strength, open-field activity
Secondary Endpoints	PK exposure: Cmax, Tmax, AUC24, brain/plasma ratio	Progressive-ratio breakpoint; extinction; cue-induced reinstatement	Extinction rate; cue- or cocaine-primed reinstatement; nucleus accumbens dopamine by HPLC	Survival; TDP-43 histology; GFAP; Iba1; motor neuron count	Iba1, GFAP, IL-1β, TNF-α, IL-6, IFNγ; NeuN; TUNEL; hypothalamic inflammation	α-synuclein aggregation, phosphorylated α-synuclein, tyrosine hydroxylase staining, dopaminergic neuron integrity
Exploratory Endpoints	REM/PS duration, SWS duration, locomotor activity, GI tolerance, body weight, fecal output	Locomotor activity; food intake; body weight; behavioral sensitization	Elevated plus maze; locomotion; body weight; anxiety-like behavior	Sleep/activity rhythm; inflammatory cytokines; mitochondrial stress markers	Orexin neuron counts where biologically applicable; microglial morphology; correlation between CTSH activity and symptom worsening	Iba1, GFAP, inflammatory cytokines, mitochondrial stress markers, sleep–wake/activity rhythm
Scientific Objective	Determine whether food intake significantly alters wake-promoting efficacy or systemic/CNS exposure	Determine whether AEX-41 and AEX-2 reduce opioid-seeking behavior without inducing nonspecific sedation	Test whether DOXA compounds attenuate cocaine-associated contextual reward without producing anxiety or motor suppression	Determine whether AEX-635/AEX-609 slow motor decline and reduce ALS-relevant biomarkers	Test whether AEX-41/AEX-2 improve narcoleptic symptoms under inflammatory stress and reduce CTSH-linked neuroinflammatory signaling	Determine whether AEX compounds modulate α-synuclein pathology and PD-relevant neurodegeneration
Mechanistic Hypothesis	A food-independent profile would support stable orexin receptor engagement and flexible real-world administration	Balanced OX1R/OX2R agonist may regulate emotional reward salience and reduce pathological drug-seeking rather than amplify reinforcement	Dual OX1R/OX2R activation may normalize reward salience and dopamine dysregulation without acting as a classical reinforcer	Sigma-1, EAAT2/AdipoR2, and orexin-related signaling may support neuronal resilience, astrocyte function, and neuroinflammatory control	DOXA compounds may combine symptomatic dual OX1R/OX2R restoration with CTSH-associated neuroinflammatory modulation	DOXA compounds may support proteostasis, reduce neuroinflammation, improve mitochondrial resilience, and preserve dopaminergic network function
Disease-Modifying Rationale	Not disease-modifying; supports clinical practicality and chronic NT1 dosing feasibility	Not disease-modifying for NT1; translational expansion into reward-circuit dysregulation and addiction vulnerability	Not disease-modifying for NT1; supports neuropsychiatric expansion and abuse-liability de-risking	Potential modulation of TDP-43 pathology, neuroinflammation, metabolic stress, and motor neuron survival	Potential transition from symptomatic orexin replacement toward protection against inflammatory orexin-neuron vulnerability	Potential to move beyond symptomatic arousal effects toward modulation of α-synuclein-driven neurodegenerative mechanisms

DOXA Platform: Translational Development Strategy Beyond NT1

The DOXA platform is a first-in-class non-sulfonamide dual OX1R/OX2R agonist platform designed to restore physiological orexin signaling while integrating broader neuroprotective, anti-inflammatory, metabolic, and CNS translational mechanisms. Unlike conventional wake-promoting approaches, DOXA aims to restore the multidimensional functions of the endogenous orexin network, including wake maintenance, REM regulation, emotional arousal, reward-circuit modulation, appetite and energy homeostasis, and global sleep–wake organization. The DOXA library currently includes 114 synthesized compounds (102 unique molecules after optimization), structured around three proprietary scaffold families: dihydro-quinazolin-4(1H)-one, dihydro-1,3-benzothiazin-4-one, and dihydro-1,3-benzoxazin-4-one derivatives (WO2024/115797 A2).

Lead compounds were designed to combine balanced dual OX1R/OX2R agonist activity with additional pharmacological dimensions including Sigma-1 modulation, DAT activity, mGluR2 signaling, and CTSH-related neuroinflammatory modulation. In vivo validation in ORX-KO narcolepsy models demonstrated that AEX-41 and AEX-2 produced robust wake promotion, major cataplexy reduction, REM modulation, SWS transition instability reduction and improved sleep–wake organization (ASCP Annual Meeting Phoenix 2025 T41).

The **DOXA preclinical development program** was specifically designed to address four major translational questions: **Does OX1R engagement increase abuse liability, or alternatively modulate reward circuitry in a manner capable of reducing addictive behaviors? Does food intake significantly alter pharmacodynamic efficacy or oral translational robustness?Can CTSH-associated neuroinflammatory pathways be modulated to support disease-modifying therapeutic strategies extending beyond symptomatic orexin replacement?**

Future development priorities include the optimization of oral bioavailability and chronic dosing formulations, the GLP-compliant ADME/Toxicology development, with a translational biomarker integration, including validation of CTSH-associated neuroinflammatory mechanisms, evaluation of neuroprotective effects in ALS and Parkinson's disease models, with exploration of addiction-related reward modulation, and metabolic disease applications.
Hybrid therapeutic strategies combining DOXA compounds with regenerative astrocytic therapies such as AstroRx® may also represent future translational opportunities for ALS and broader neurodegenerative disorders.